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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/845,006	04/27/2001	Hansgeorg Schindler	SONN:010US/MBW	1473

7590 02/23/2005

Mark B. Wilson
Fulbright & Jaworski L.L.P.
600 Congress Avenue, Suite 2400
Austin, TX 78701

EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 02/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/845,006	SCHINDLER, HANSGEORG	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-45 and 61* is/are pending in the application.

4a) Of the above claim(s) *41 and 43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-40,42,44,45 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/26/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination (RCE)

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection (e.g., see 9/23/04 Response). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/26/04 has been entered. Claims 24-45 and 61 were pending. No claims were added or amended. Therefore, claims 24-45 and 61 are still currently pending. Claims 41 and 43 remain withdrawn because they read on non-elected species and/or inventions and thus these claims remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim. Therefore, claims 24-40, 42, 44, 45 and 61 are examined on the merits in this action.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Withdrawn Objections/Rejections

2. The rejection under 35 U.S.C. 112, second paragraph denoted I is withdrawn in view of Applicant's arguments and/or amendments. The rejection under 35 U.S.C. 112, first paragraph is withdrawn in view of Applicant's amendments and/or arguments. The Steyer et al. and Eriksson et al. rejections under 35 U.S.C. 102 are withdrawn in view of Applicant's priority document submission and/or arguments. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claims Rejections - 35 U.S.C. 112, second paragraph

3. Claims 26 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Withdrawn.

B. Withdrawn.

C. Withdrawn.

D. Withdrawn.

E. Withdrawn.

F. Withdrawn.

G. For **claim 26**, the term "equal marker" is vague and indefinite. For example, it is not clear what "equal" refers to i.e., there is no basis for determining the equality? For example, does Applicant mean that the "markers" are "equal" because they have the same structure? Does Applicant mean that the "markers" the "equal" because they fluoresce with "equal" intensity or provide emit an "equal" wavelength of light? Applicants are requested to clarify. Therefore, claims 26 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

H. Withdrawn.

Response

4. Applicant's arguments directed to the above 35 U.S.C. 112, second paragraph rejections were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or newly amended arguments.

G. Applicant argues, "this term [simply denotes] that all of the marker molecules in the sample are the same, i.e., that the markers are 'equal' in the sense of structural identity and wavelength-specific identity" (e.g., 1/26/2004 Response, page 10, last paragraph).

This is not found persuasive for the following reasons:

The Examiner respectfully disagrees. The definition set forth by Applicants in the 7/26/04 Response wherein an equal marker allegedly refers to (1) structural identity and (2) wavelength-specific identity is not supported by the specification. For example, Applicants recited passage (e.g., page 23, line 17 through page 24, line 5) never even mentions the term "equal marker" and also does not refer to this new two-prong test (i.e., structural and wavelength specificity).

Accordingly, the 35 U.S.C. 112, second paragraph rejections cited above are hereby maintained.

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 24-28, 30-34 and 61 are rejected under 35 U.S.C. 102(b) as being anticipated by Sharonov et al. (Sharonov, S.; Chourpa, I.; Morjani, H.; Nabiev, I.; Manfait, M. "Confocal spectral imagining analysis in studies of the spatial distribution of antitumor drugs within living cancer cells" *Analytica Chimica Acta* 290 (1994) 40-47.).

For ***claims 24 and 61***, Sharonov et al. (see entire document) disclose an apparatus for confocal spectral imaging analysis (see Sharonov et al, abstract; see also figure 2), which anticipates claims 24 and 61. For example, Sharonov et al. disclose at least one source of light adapted to fluorescently excite, via single or multiple photon absorption marker molecules in said sample (e.g., see figure 2, element 1 wherein a laser (Spectra-Physics Model 2026) is disclosed as the light source; see also abstract wherein both bound and unbound doxorubicin and mitoxantrone are disclosed and the marker molecules inside the K562 cancer cells; see also figures 4-5). Sharonov et al. do not explicitly state that the light source is adapted for large-area fluorescent excitation, but the Examiner contends that this would be an inherent property of the laser because Applicants' most preferred embodiment for large-area fluorescent excitation is a laser (e.g., see

specification, page 7, middle paragraph, "only the source of light needs to be suitable for large-area fluorescence excitation. Here, a preferred source of light is a laser"; see also claim 34) (emphasis added). Moreover, Sharonov et al. disclose the excitation of a 20 × 20 μm region (e.g., see Sharonov et al., page 42, column 1, last paragraph), which falls within Applicants' most preferred range of 100 to 10,000 μm^2 (e.g., see specification, page 7, middle paragraph, "the large-area fluorescence excitation, preferably 100 to 10,000 μm^2, depending on the application"; see also 35 U.S.C. § 112, second paragraph rejection below) because $20 \times 20 = 400\ \mu m^2$, which is between 100 to 10,000 μm^2. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). In addition, it is not clear what is meant by the term "large-area" fluorescence (e.g., see 35 U.S.C. § 112, second paragraph rejection below).

In addition, Sharonov et al. disclose a sample holder (e.g., see figure 2, element 5). Sharonov et al. also disclose a detection and analysis system comprising a charged coupled device (CCD) camera (e.g., see figure 2, element 8). Sharonov et al. also disclose a detection and analysis system and a sample holder that are movable laterally relative to each other during use (e.g., see figure 2, elements 2 and 6; see also page 42, last paragraph, "The sample compartment is

moved with an automatic scanning stage ... and can be scanned along the y-axis [i.e., laterally] with a minimum step size of 0.1 um. The scanning of the sample along the x-axis is achieved by the optical scanner being installed in the confocal entrance chamber"). Sharonov et al. also disclose a control unit that is adapted to coordinate and synchronize illumination times and lateral movement between said sample holder and said detection and analysis system (e.g., see figure 2, elements 6 and 9; see also page 42, column 1, paragraph 2 wherein an IBM PC/AT-486 is disclosed, "The scanning of the sample stage and mirrors of the optical scanner and all operations connected with recording of spectra are computer-controlled (IBM PC/AT-486) by the ImageSoft software through the net-work between the IBM PC/AT and the RISC 6000 work station"; see also page 42, column 2, paragraphs 2-5; see also figure 3).

For ***claim 25***, Sharonov et al. disclose an apparatus that can visualize interactions between molecules and molecular processes in biological cells (e.g., see figure 4, especially figure 4c-d wherein drug binding interactions were demonstrated for mitroxantrone in the nuclear inclusions).

For ***claim 26***, Sharonov et al. disclose equal marker molecules (e.g., see figure 4 wherein mitroxantrone is shown in both the nuclear membrane and in the cytoplasm, DNA-bound mitroxantrone is also shown; see also maintained 35 U.S.C. 112, second paragraph rejection).

For ***claim 27***, Sharonov et al. disclose different marker molecules (e.g., see figure 4 wherein both "bound" and "unbound" mitroxantrone are shown;

compare also figures 4-5 wherein both doxorubicin and mitoxantrone are used; see also figure 1; see also maintained 35 U.S.C. 112, second paragraph rejection).

For ***claim 28***, Sharonov et al. disclose adjusting the wavelength during use from 457.9 to 514.5 nm (e.g., see page 42, column 2, paragraph 1).

For ***claim 30***, Sharonov et al. disclose 20 μm × 20 μm = 400 μm^2 (e.g., see Sharonov et al., page 42, column 1, last paragraph).

For ***claim 31***, Sharonov et al. disclose a control unit that is adapted to coordinate and synchronize positioning and shifting of images to each sample position on a pixel array of said CCD camera (e.g., see page 41, column 2, second to last paragraph; see also page 42, column 2, paragraphs 2-3; see also page 43, column 1, paragraph 2).

For ***claims 33-34***, Sharonov et al. disclose an acousto-optically switchable laser (e.g., see figure 2, element 1; see also page 42, paragraph bridging columns 1-2 wherein a switchable Spectra-Physics Model 2026 is disclosed).

Response

6. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicant argues, "Sharonov et al. cannot anticipate the present claims because it does not teach "at least one source of light adapted for large-area fluorescent excitation, via single or multiple photon absorption, of marker molecules in said sample during use" (e.g., see 7/26/04 Response, pages 10-11, especially page 11, paragraph 1).

[2] Applicants argue, "it would be clear to one of skill reading Sharonov et al. that the apparatus described therein is not useful to 'visualize molecules, movements of molecules, interactions between molecules, and molecular processes'" (e.g., see 7/26/04 Response, page 11, paragraph 2).

This is not found persuasive for the following reasons:

[1] The Examiner contends that it is not clear what "large-area" fluorescent excitation means and, as a result, Applicant's arguments are moot (e.g., see 35 U.S.C. 112, second paragraph rejection below). In addition, the laser used by Sharonov et al. falls within the most preferred embodiments for large-area excitation and, as a result, the Sharonov et al. reference inherently discloses this feature (see newly modified rejection above).

[2] In response to applicant's arguments, the recitation "visualize molecules, movements of molecules, interactions between molecules, and molecular processes," has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

In addition, the Examiner notes that Applicants' arguments are not commensurate in scope with the claims. A laser can clearly be used for BOTH confocal and wide-field microscopy (e.g., see specification wherein the laser is denoted as Applicants' preferred embodiment for large-area fluorescence). Thus, Applicants claims would encompass the laser disclosed by Sharonov et al.

Accordingly, the 35 U.S.C. §102(b) rejection cited above is hereby maintained.

New Rejections

Claims Rejections - 35 U.S.C. 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

7. Claim 25 is rejected under 35 U.S.C. 101 because the claim is directed to non-statutory subject matter. Independent claim 24 is drawn to an apparatus "for visualizing molecules" and dependent claim 25 further comprises a product described as "biological cells" which are placed into said apparatus (e.g., see claim 25; see also Applicants' 7/26/04 arguments, page 8, first full paragraph). Thus, claim 25 is drawn to two statutory classes of invention (i.e., a product and an apparatus), rather than a single statutory class of invention. This is not permissible. For example, see MPEP § 2173.05(p), "Such claims should ... be rejected under 35 U.S.C. 101 based on the theory that the claim ... embraces or overlaps two different statutory classes of invention set forth in 35 U.S.C. 101 which is drafted so as to set forth the statutory classes of invention in the alternative only" (emphasis added).

The Examiner concedes that there are situations where claims are permissively drafted to include a reference to more than one statutory class of invention (e.g., see MPEP § 2173.05(p) disclosing "product-by-process" claims), but the Examiner notes that those situations are only permissible because Applicants make clear that the "product" and NOT the "process" is being claimed (e.g., see MPEP § 2173.05(p), "A claim to a device, apparatus, manufacture, or composition of matter may contain a reference to the process in which it is intended to be used without being objectionable under 35 U.S.C. 112, second paragraph, so long as it is clear that the claim is directed to the product and not the process") (emphasis added). Here, it would appear that both the "apparatus" and the "product" are simultaneously being claimed (e.g., see Applicant's 7/26/04 Response, page 8, first full paragraph).

Claims Rejections - 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 24-40, 42, 44, 45 and 61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

AA. ***Claim 25*** is indefinite because Applicant is claiming more than one statutory class of invention in the same claim. For example, Applicants state in their 7/26/04 Response, "... [claim 25] requires that biological cells be present in

the sample holder .... further limit[ing] claim 24" (e.g., see 7/26/04 Response, page 8, first full paragraph). Thus, Applicants are clearly trying to claim both a "product" (i.e., the biological cells) and an "apparatus" (i.e., the arrangement adapted for the visualization of said cells) in the same claim. This is not permissible. For example, see *In Ex parte Lyell* wherein the Court struck down a claim drawn to two statutory classes of invention, 17 USPQ2d 1548 (Bd. Pat. App. & Inter. 1990) (a claim directed to an automatic transmission workstand and the method steps of using it was held to be ambiguous and properly rejected under 35 U.S.C. 112, second paragraph). See more generally MPEP § 2173.05(p).

Please note that other "statutory hybrid" claims are not rejected like product-by process claims because Applicants make clear what is being claimed i.e., the product and NOT the process (see MPEP § 2173.05(p), "A claim to a device, apparatus, manufacture, or composition of matter may contain a reference to the process in which it is intended to be used without being objectionable under 35 U.S.C. 112, second paragraph, so long as it is clear that the claim is directed to the product and not the process") (emphasis added). That is not the case here. To the contrary, Applicants have made it clear that both the "apparatus" and the "product" are being claimed simultaneously (e.g., see 7/26/04 Response, page 8, first full paragraph).

BB. ***Claim 24*** recites "large-area" fluorescence excitation. The term "large-area" is a relative term, which renders the claim indefinite and/or unclear. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be

reasonably apprised of the scope of the invention. See also MPEP § 2173.05(b). The Examiner notes that Applicant's specification states, "Due to the large-area fluorescence excitation, preferably 100 to 10,000 μm^2, depending on the application, imaging of the excited molecules may be very rapid" (see page 7, paragraph 2). However, this statement is merely exemplary in nature and does not further limit the term "large" to a range from 100 to 10,000 μm^2 and, as a result, it is not clear to what extent the term "large" could extend beyond this limit (e.g., would 90 μm^2 infringe, 80 μm^2 infringe, etc). Thus, the metes and bounds of the claimed invention cannot be determined. Therefore, claim 24 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

Response

9. Applicant's arguments directed to the above 35 U.S.C. 112, second paragraph rejection denoted BB were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons.

BB. Applicant argues, "... the term 'large-area fluorescent excitation' is used to distinguish and delimit the present invention, which relates to an arrangement for the practice of a 'wide-field microscopy' technique, from arrangements for the practice of 'confocal microscopy' techniques. Those of skill will understand the differences between confocal and wide-field imaging" and cites a reference by Peter J. Shaw in support of this position.

This is not found persuasive for the following reasons:

The Examiner respectfully disagrees. The Peter J. Shaw reference never mentions the term "large-area" fluorescence. In addition, the specification never mentions that "large-area" fluorescence is being used to distinguish between confocal and wide-field imagining. Therefore, Applicant's argument is not supported in fact. In addition, Applicant's most preferred embodiment for large-area fluorescence is a laser (e.g., see specification, page 7, middle paragraph, "... only the source of light needs to be suitable for large-area fluorescence excitation. Here, a preferred source of light is a laser") (emphasis added), which is exactly what is being allegedly impermissibly disclosed by Sharonov et al. (e.g., see 35 U.S.C. 102(b) rejection above and Response to Applicant's arguments). Consequently, it is not clear how Applicant's laser differs from the laser disclosed by Sharonov et al. Thus, the metes and bounds of the claimed invention cannot be determined.

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 24, 26, 27, 30, 32, 34, 35, 37 and 61 are rejected under 35 U.S.C. 102(b) as being anticipated by Sanchez et al. (Sanchez, E. J.; Novotny, L.; Holtom, G. R.; Xie,

S. "Room-Temperature Fluorescence Imaging and Spectroscopy of Single Molecules by Two-Photon Excitation" *Journal of Physical Chemistry A* **September 18, 1997**, *101(38)* 7019-7023) (10/23/03 IDS, Reference C8).

For ***claims 24***, Sanchez et al. (see entire document) disclose an apparatus for room temperature fluorescence imagining and spectroscopy of single molecules by two-photon excitation, which anticipates the claimed invention (e.g., see abstract; see also figure 1). For example, Sanchez et al. disclose at least one source of light adapted for large-area fluorescence, via single or multiple photon absorption, of marker molecules in said sample during use (e.g., see figure 1 wherein Argon Ion laser is disclosed; see also Experimental section, paragraph 1 wherein a Ti-sapphire "two-photon" excitation laser is disclosed). Sanchez et al. do not explicitly state that the light source is adapted for large-area fluorescent excitation, but the Examiner contends that this would be an inherent property of the laser because Applicants' most preferred embodiment for large-area fluorescent excitation is a laser (e.g., see specification, page 7, middle paragraph, "only the source of light needs to be suitable for large-area fluorescence excitation. Here, a preferred source of light is a laser"; see also claims 32 and 34; see also page 13 of Applicant's specification wherein the method of Sanchez was disclosed as a preferred embodiment) (emphasis added). Moreover, Sanchez et al. disclose the excitation of a $10 \times 10\ \mu m^2$ region = $100\ \mu m^2$ (e.g., see Sanchez et al., page 42, column 1, last paragraph), which falls within Applicants' most preferred range of 100 to 10,000 μm^2 (e.g., see specification, page 7, middle

paragraph, "the large-area fluorescence excitation, preferably 100 to 10,000 μm^2, depending on the application"; see also 35 U.S.C. § 112, second paragraph rejection below). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). In addition, it is not clear what is meant by the term "large-area" fluorescence (e.g., see 35 U.S.C. § 112, second paragraph rejection below).

In addition, Sanchez et al. disclose a sample holder (e.g., see figure 1 wherein the sample holder is labeled). Sanchez et al. also disclose a detection and analysis system comprising a charged coupled device (CCD) camera (e.g., see figure 1 wherein the CCD camera is labeled; see also page 7021, column 2, last paragraph; see also Experimental section wherein a Nikon Diaphot 300 inverted epifluorescent microscope is disclosed). Sanchez et al. disclose a detection and analysis system wherein at least one of the sample holder and the detection and analysis system is moveable laterally, relative to the other during use (e.g., see figure 1 wherein XY scanbed is disclosed). Finally, Sanchez et al. disclose a control unit adapted to coordinate and synchronize illumination times and lateral movement between said sample holder and said detection and analysis system during use (e.g., see Experimental Section, last paragraph, wherein "a modified

Nanoscope IIIA controller was used for controlling the scan bed and image acquisition"; see also figure 1; see also Introduction wherein Applicant's intended use in the preamble for "visualizing molecules, movements of molecules, interactions between molecules and molecular processes are disclosed).

For ***claim 26***, Sanchez et al. disclose, for example, "equal" RhB dye marker molecules (e.g., see Figure 2)

For ***claim 27***, Sanchez et al. disclose do not disclose the use of "different marker molecules, but this limitation has not been given any patentable weight because it represents intended use only. If the prior art structure is capable of performing the intended use, then it meets the claim. The Office does not have the facilities to make a comparison and the burden is on the applicants to establish any difference between the transducing elements of the art and the instant claims. Se In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For ***claim 30***, Sanchez et al. disclose $10 \times 10\ \mu m = 100\ \mu m^2$ (e.g., see Sanchez et al. page 7022, column 2, paragraph 1).

For ***claims 32 and 34***, Sanchez et al. disclose, for example, an argon laser and/or a "two-photon" excitation laser (e.g., see figure 1; see also Experimental section).

For ***claim 35***, Sanchez et al. disclose a control unit that further comprises a pulse transmitter and a software adapted to control said at least one source of light and said movement of said sample holder during use (e.g., see Sanchez et al., figure 1; see also Experimental section, paragraph 3, wherein Nanoscope IIIA

controller is used for "controlling the scan bed and image acquisition"; see also paragraph 1 wherein 100 fs pulses are disclosed).

For ***claim 37***, Sanchez et al. disclose an inverted epifluorescence microscope (e.g., see Experimental section).

For ***claim 61***, Sanchez et al. disclose lateral movement (e.g., see figure 1, XY scanbed).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under

37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 24, 26, 27, 29, 30, 32, 34, 35, 37, 44 and 61are rejected under 35 U.S.C. 103(a) as being unpatentable over Sanchez et al. (Sanchez, E. J.; Novotny, L.; Holtom, G. R.; Xie, S. "Room-Temperature Fluorescence Imaging and Sepctroscopy of Single Molecules by Two-Photon Excitation" *Journal of Physical Chemistry A* **September 18, 1997**, *101(38)* 7019-7023) (10/23/03 IDS, Reference C8) and Lewis et al. (U.S. Patent No. 5,705,878) (Date of Patent is **January 6, 1998**).

For ***claims 24, 26, 27, 30, 32, 34, 35, 37 and 61***, Sanchez et al. teach all the limitations stated in the 35 U.S.C. 102(b) rejection above (incorporated in its entirety herein by reference), which anticipates and, as a result, renders obvious claims 24, 26, 27, 30, 32, 34, 35, 37 and 61.

The prior art teaching of Sanchez et al. differs from the claimed invention as follows:

For ***claim 29***, the prior art teachings of Sanchez et al. differ from the claimed invention by not specifically reciting the use of both horizontal (x an y direction) and vertical (z direction) control.

For ***claim 44***, the prior art teachings of Sanchez et al. differ from the claimed invention by not reciting the use of a piezo element.

However, Lewis et al. teach the following limitations that are deficient in Sanchez et al.:

For ***claim 29***, Lewis et al. (see entire document) teach that x, y and z control using an automated flat scanning stage (e.g., see Lewis et al., Summary of the Invention; see also column 3, lines 24-28, "Lateral (X-Y) scanning of frame 30 is performed by using the piezo tubes in pairs while axial positioning in a direction (Z) perpendicular to the X,Y plane is provided by using all four tubes simultaneously"; see also figures 1-4).

For ***claim 44***, Lewis et al. teach the use of a piezo element (e.g., see Lewis et al., Summary of the Invention; see also figures 1, 2 and 4; see also column 3, lines 24-28, "Lateral (X-Y) scanning of frame 30 is performed by using the piezo tubes in pairs while axial positioning in a direction (Z) perpendicular to the X,Y plane is provided by using all four tubes simultaneously").

It would have been obvious to one skilled in the art at the time the invention was made to use the fluorescence imaging and spectroscopy apparatus as taught by Sanchez et al. with the automated flat scanning XYZ stage as taught by Lewis et al. because Lewis et al. explicitly states that their "flat design" is "particularly well suited for ... confocal optical microscopy" (e.g., see Lewis et al., column 1, lines 11-14), which would encompass the confocal microscopy apparatus disclosed by Sanchez et al. (e.g., see Sanchez et al., Introduction). Furthermore, one of ordinary skill in the art would have been motivated to use the piezo XYZ stage disclosed by Lewis et al. because Lewis et al. explicitly state that their invention is "ideally suited for stage scanning confocal optical

microscopy. Its inherent axial positioning capability provides a mechanism for optically slicing s ample in the z direction while scanning it through the confocal spot" (e.g., see Lewis et al., column 2, lines 40-45; see also paragraph bridging columns 3-4, "The principle advantage of the present scanner over previous geometries is that the three-dimensional scanning is accomplished in a flat thin plate which can be readily placed close to a high power microscope objective"). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Lewis et al. teach that their stage is compatible with all types of microscopes and especially with confocal microscopy disclosed by Sanchez (see Lewis et al., Summary of Invention; see also column 4, paragraph 1, "Since the scanner does not extend below the plane of the plate, the objective is completely free to be exchanged by the simple rotation mechanisms found in all optical microscopes").

14. Claims 24-40, 42, 44, 45 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmidt et al. (Schmidt, T. H.; Schutz, G. J.; Baumgartner, W.; Gruber, H. J.; Schindler, H. "Imaging of single molecule diffusion" PNAS 1996, 93, 2926-2929) (of record) and Lewis et al. (U.S. Patent No. 5,705,878) (Date of Patent is **January 6, 1998**) as evidenced by Schmidt et al. (Schmidt, T. H.; Hinterforfer, P.; Schnidler, H. "Microscopy for Recognition of Individual Molecules" *Laser und Optoelektronik* **1997**, *29(1)*, 56-62) (referred to herein as "Schmidt 1997") and Albertine et al. (e.g., see Albertine, K. H.; Cerasoli, F.; Gee M. H.; Ishihara, Y.; Tahamont, M. V.; Gottlieb, J. E.; Peters, S. P. "Morphological analysis of the activation of adherent

neutrophils in vitro" *Tissue Cell* **1998** *20(4)*, 519-530) and Al-Ghoul et al. (Al-Ghoul, K. J.; Costello, M. J.; "Light Microscopic Variation of Fiber Cell Size, Shape and Ordering in the Equatorial Plane of Bovine and Human Lenses" Molecular Vision 1997, 3, 2).

For ***claim 24***, Schmidt et al. (see entire document) teach a method for imaging single molecule diffusion (e.g., see Schmidt et al., abstract), which reads on the claimed invention. For example, Schmidt et al. teach the use of at least one source of light adapted for large-area fluorescent excitation, via single or multiple photon absorption, of marker molecules in said sample during use (e.g., see Schmidt et al., page 2926 wherein an argon-laser is disclosed, "For this, we used epifluorescence microscopy with argon-ion laser excitation and imaging onto a highly-sensitive liquid-nitrogen-cooled CCD-camera"; see also figure 1). In addition, Schmidt et al. teach a sample holder (e.g., see page 2927, column 1, paragraph 2 wherein samples are immobilized on a cover-slip). Schmidt et al. also disclose a detection and analysis system comprising a charged coupled device (CCD) camera (e.g., see Schmidt et al., page 2926 wherein an epifluorescence microscope equipped with a nitrogen-cooled CCD camera is disclosed, "For this, we used epifluorescence microscopy with argon-ion laser excitation and imaging onto a highly-sensitive liquid-nitrogen-cooled CCD-camera"). Finally, Schmidt et al. disclose a control unit adapted to coordinate and synchronize illumination times (e.g., see Schmidt et al., page 2926-2927 wherein a CCD camera equipped with a TH512B chip is disclosed "... provid[ing] trigger pulses for the acousto-optic modulator for repeated illuminations").

For ***claim 25***, Schmidt et al. disclose the use of biological cells (e.g., see Schmidt et al., page 2929, Conclusion).

For ***claims 26-27***, a recitation directed to the manner in which a claimed apparatus is intended to be used does not distinguish the claimed apparatus from the prior art – if the prior art has the capability to so perform. See MPEP 2114 and *Ex parte Masham*, 2 USPQ2d 1647 (Bd. Pat. App. & Inter. 1987). Here, Applicants use of equal or different markers does not impart any patentably distinct features on the apparatus and thus is not given any patentable weight in accordance with MPEP § 2114. However, even if assuming arguendo the use of said sample markers were to be given patentable weight, Schmidt et al. disclose both equal and different marker molecules (e.g., Materials and Methods section wherein equal TRITC DHPE molecules are disclosed; see also bell curve in figure 2 showing some "markers" with less than 100 counts and some with greater than 300 counts i.e., different markers; see also Conclusion wherein different markers are disclosed).

For ***claim 28***, Schmidt et al. disclose the coordination and synchronization of 5 ms Gaussian-shaped laser beam pulses of 6.1 μm width and 57 kW/cm2 mean excitation intensity taken at 35 ms intervals (e.g., see figures 1 and 3).

For ***claim 30***, Schmidt et al. do not explicitly state that their laser will excite a range from 100 to 10,000 μm^2, but the Examiner contends that this level of excitation would be an inherent property of the laser because Applicants' most preferred embodiment for large-area fluorescent excitation is a laser (e.g., see specification, page 7, middle paragraph, "only the source of light needs to be

suitable for large-area fluorescence excitation. Here, a preferred source of light is a laser"; see also claim 32) (emphasis added). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). In addition, it is not clear what is meant by the term "large-area" fluorescence (e.g., see 35 U.S.C. § 112, second paragraph rejection below).

For ***claim 31***, Schmidt et al. disclose positioning and shifting of images using a "frameshift" CCD camera equipped with both (1) acquisition and (2) storage functional capabilities and the ability to "synchronize" and "coordinate" between these two functions.

For ***claims 32 and 34***, Schmidt et al. disclose an argon-ion laser (e.g., see Schmidt et al., page 2926, column 1, paragraph 1).

For ***claim 33***, Schmidt et al. disclose an acousto-optically switchable laser light (e.g., see Schmidt et al., page 2927, column 1, paragraph 1, "The camera provided trigger pulses for the acoustoptic modulator for repeated illuminations").

For ***claim 35***, Schmidt et al. disclose a pulse transmitter and mechanism for controlling said transmitter wherein the laser can generate 5 ms pulses (e.g., see Schmidt et al., Materials and Methods section; see also page 2927, column 1,

paragraph 1, "The camera provided trigger pulses for the acoustoptic modulator for repeated illuminations").

For ***claim 36***, Schmidt et al., disclose both "continuous" and "frameshift" CCD modes (e.g., see Schmidt et al., page 2926, column 2, last paragraph).

For ***claim 37***, Schmidt et al., disclose an epifluorescence microscope (e.g., see page 2926, column 1, last paragraph, "For this, we used epifluorescence microscopy with argon-ion laser excitation and imaging onto a highly-sensitive liquid-nitrogen-cooled CCD-camera"; see also Materials and Methods section).

For ***claim 38***, Schmidt et al. disclose and efficiency of 3% (e.g., see Schmidt et al., page 2926, column 1, last paragraph).

For ***claim 39***, Schmidt et al. disclose a N_2 cooled CCD camera with a large pixel array and noise of only a few electrons per pixel (e.g., see page 2926, column 1, last paragraph, "For this, we used epifluorescence microscopy with argon-ion laser excitation and imaging onto a highly-sensitive liquid-nitrogen-cooled CCD-camera"; see also Materials and Methods section wherein 4 counts/pixel read-out noise is disclosed). Schmidt et al. do not disclose the quantum efficiency or dark counts of their SDT system. The reference is silent on the issue. However, the Examiner contends that these features would be an inherent property of the system as disclosed by a later paper by Schmidt et al. (referred to herein as "Schmidt 1997") referring back to the previous studies (e.g., see Schmidt 1997, translation, page 7, Figure 1B shows the setup for single molecule detection with a conventional epifluorescence microscope and a nitrogen-cooled CCD camera (4cnts readout noise, dark counts negligible,

quantum efficiency 0.8 electrons/photon)"; please note that reference [12] refers to the previous Schmidt et al. article published in 1996).

For ***claim 45***, Schmidt et al discloses the same Axiovert 135-TV Zeiss microscope as that disclose in Applicant's preferred embodiments (e.g., see Example 1 in Specification) and, as a result, must possess the same parallel beam region. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

The prior art teachings of Schmidt et al. differ from the claimed invention as follows:

For ***claims 29 and 35***, Schmidt et al. are deficient in that they do not specifically teach the use of an XYZ stage for automated lateral and vertical movements. Schmidt et al. is silent on the issue.

For ***claim 40***, Schmidt et al. are deficient in that they do not teach the use of a pixel array > 1340 × 1300.

For ***claim 42***, Schmidt et al. are deficient in that they do not teach the use of a microtiter plate.

For ***claim 44***, Schmidt et al. are deficient in that they do not teach the use of a piezo element used in conjunction with the XYZ stage for Z moments.

However, Lewis et al. teach the following limitations that are deficient in Schmidt et al.:

For ***claims 29 and 35***, Lewis et al. (see entire document) teach that x, y and z control using an automated flat scanning stage (e.g., see Lewis et al., Summary of the Invention; see also column 3, lines 24-28, "Lateral (X-Y) scanning of frame 30 is performed by using the piezo tubes in pairs while axial positioning in a direction (Z) perpendicular to the X,Y plane is provided by using all four tubes simultaneously"; see also figures 1-4).

For ***claim 40***, Al-Ghoul et al. teach the use of a pixel array that is 2048 × 2048 (e.g., see page 2, column 2, paragraph 2).

For ***claim 42***, Albertine et al. teach the use of a microtiter plate for use in microscopy of biological samples for "parallel" screening and identification (e.g., see Albertine et al., abstract).

For ***claim 44***, Lewis et al. teach the use of a piezo element (e.g., see Lewis et al., Summary of the Invention; see also figures 1, 2 and 4; see also column 3, lines 24-28, "Lateral (X-Y) scanning of frame 30 is performed by using the piezo tubes in pairs while axial positioning in a direction (Z) perpendicular to the X,Y plane is provided by using all four tubes simultaneously").

It would have been obvious to one skilled in the art at the time the invention was made to use the single dye tracing apparatus as taught by Schmidt et al. with the automated flat scanning XYZ stage as taught by Lewis et al. because Lewis et al. explicitly states that their "flat design" is "particularly well suited for ... microscopy" (e.g., see Lewis et al., column 1, lines 11-14), which

would encompass the confocal microscopy apparatus disclosed by Schmidt et al. (e.g., see Schmidt et al., Introduction). Furthermore, one of ordinary skill in the art would have been motivated to use the piezo XYZ stage disclosed by Lewis et al. because Lewis et al. explicitly state, "The principle advantage of the present scanner over previous geometries is that the three-dimensional scanning is accomplished in a flat thin plate which can be readily placed close to a high power microscope objective" (e.g., see Lewis et al., column 2, lines 40-45; see also paragraph bridging columns 3-4), which would encompass the microscope objective disclosed by Schmidt et al. Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Lewis et al. teach that their stage is compatible with all types of microscopes (see Lewis et al., Summary of Invention; see also column 4, paragraph 1, "Since the scanner does not extend below the plane of the plate, the objective is completely free to be exchanged by the simple rotation mechanisms found in all optical microscopes").

In addition, a person of skill in the art would have been motivated to use the microtiter plates disclosed by Albertine et al. with the single dye tracing apparatus as disclosed by Schmidt et al. because Albertine et al. explicitly states that their microtiter plates can be used with microscopy (e.g., see Albertine et al., abstract). Furthermore, a person of skill in the art would have been motivated to use a microtiter plate to prepare and/or test samples in "parallel" i.e., to save time. Furthermore, a person of skill in the art would have reasonably been expected to be successful because Albertine et al. show that microtiter plates can be used in conjunction with microscopes.

Finally, a person of skill in the art would have been motivated to use the 2048 × 2048 pixel array to replace the smaller arrays disclosed by Schmidt et al. because this array is designed to collect images in the same manner as the smaller arrays (i.e., the references represent analogous art). A person of skill in the art would have been motivated to use the array disclosed by Al-Ghoul et al. because it possesses higher resolution (i.e., 2048 × 2048). A person of skill would have reasonably been expected to be successful because the array is used in a CCD camera just as is the case for Schmidt et al.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
January 19, 2005

ANDREW WANG
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600